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Efficacy of dose-escalated chemoradiation on complete tumour response in patients with locally advanced rectal cancer (RECTAL-BOOST); a phase 2 randomised controlled trial

Running title: Dose-escalated chemoradiation in rectal cancer

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Declaration of interests

We declare no competing interests.

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Data sharing statement:

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

ABSTRACT

Purpose: Pathological complete tumour response following chemoradiation in patients with locally advanced rectal cancer (LARC) is associated with favourable prognosis and allows organ-sparing treatment strategies. We aimed to investigate the effect of an external radiation boost to the tumour prior to chemoradiation on pathological or sustained clinical complete tumour response in LARC.

Methods and materials: This multicentre, non-blinded, phase 2, randomised controlled trial followed the trials within cohorts-design, which is a pragmatic trial design allowing cohort participants to be randomized for an experimental intervention. Patients in the intervention group are offered the intervention (and can accept or refuse this), whereas patients in the control group are not notified about the randomisation. Participants of a colorectal cancer cohort referred for chemoradiation of LARC to either of two radiotherapy centres were eligible. Patients were randomised to no boost or an external radiation boost (5 x 3 Gy) without concurrent chemotherapy directly followed by standard pelvic chemoradiation (25 x 2 Gy with concurrent capecitabine). The primary outcome was pathological complete response (pCR, i.e. ypT0N0) in patients with planned surgery at 12 weeks or, as surrogate for pCR, a 2-year sustained clinical complete response for patients treated with an organ preservation strategy. Analyses were intention to treat. The study was registered with ClinicalTrials.gov, number NCTXXXXXX.

Results: Between Sept 2014 and July 2018, 128 patients were randomised. Fifty-one of the 64 (79.7%) patients in the intervention group accepted and received a boost. Compared with the control group, fewer patients in the intervention group had a cT4-stage and a low rectal tumour (31.3% versus 17.2% and 56.3% versus 45.3% respectively), and more patients had a cN2-stage (59.4% versus 70.3% respectively). Rate of pathological or sustained clinical

complete tumour response was similar between the groups: 23 of 64 (35.9%, 95%CI 24.3-48.9) in the intervention group versus 24 of 64 (37.5%, 95%CI 25.7-50.5) in the control group (OR=0.94 95%CI 0.46-1.92). Near-complete or complete tumour regression was more common in the intervention group: 34 of 49 (69.4%) versus 24 of 53 (45.3%) in the control group (OR=2.74, 95%CI 1.21-6.18). Grade ≥3 acute toxicity was comparable: 6 of 64 (9.4%) in the intervention group versus 5 of 64 (7.8%) in the control group (OR=1.22 95%CI 0.35-4.22).

Conclusion: Dose escalation with an external radiotherapy boost to the tumour prior to neoadjuvant chemoradiation did not increase the pathological or sustained clinical complete tumour response rate in LARC.

Introduction

Chemoradiation prior to a total mesorectal excision (TME) in patients with locally advanced rectal cancer (LARC) reduces the risk of local recurrence and leads to downsizing of the tumour.[1,2] In 12-31% of the LARC patients, no residual tumour is found in the resected specimen after chemoradiation, defined as a pathological complete response (pCR).[3–5]

A pCR is associated with a lower risk of recurrence and longer disease-free and overall survival.[6] Moreover, TME could potentially have been omitted, thereby avoiding postoperative complications and surgery-related morbidity. It has been shown that a watch-and-wait (W&W) approach with regular surveillance in patients with a clinical complete response is a feasible alternative to TME.[7–9]

Higher radiation doses are associated with a higher probability of pathological tumour regression, as scored with the Mandard tumour regression grade.[10,11] Dose-escalated radiotherapy may therefore enhance tumour downsizing and render more patients eligible for W&W. In a systematic review on the effect of dose escalation to ≥60 Gy in LARC, a higher pooled pCR rate of 20.4% with acceptable grade ≥3 acute toxicity rate of 10.3% compared with standard chemoradiation.[12] Nevertheless, these results were predominantly based on non-randomised studies.

In the present trial, the effect of dose-escalated chemoradiation was compared with standard chemoradiation on pathological or sustained clinical complete tumour response (i.e. a combined outcome of pCR and 2-year sustained clinical complete response in organ preservation strategies) in patients with LARC.

Methods

Study design

XXXXX was a pragmatic, multicentre, non-blinded, screening phase 2, randomised controlled trial performed in two regional radiotherapy centres (XXX and XXX), as described previously.[13] XXXXX followed the pragmatic Trials within Cohorts (TwiCs) design and was conducted within the prospective data collection initiative on colorectal cancer (XXXXX) cohort.[14,15] In XXXXX, clinical data is collected from adult patients with colorectal cancer of all stages. Participants optionally consent to bio-banking (blood and/or tissue), questionnaires on patient reported outcomes (PROs), and broad consent for randomisation for future experimental interventions which means that patients can be randomised into trials embedded within the cohort in the (near) future. Only those assigned to the intervention group are informed about the trial and will be offered the intervention, which they can accept or refuse. Participants assigned to the control group are not notified about the trial, receive treatment as usual, and their clinical data is used comparatively within the trial. The TwiCs design in the XXXXX was evaluated and described in a separate publication.[16] Ethical approval for XXXXX and XXXXX were obtained from the Institutional Review Board (IRB) and the IRB of participating institutions. The study was done in accordance with the trial protocol, Good Clinical Practice guidelines, and the Declaration of Helsinki.

Patients

Eligible patients were cohort participants, who had given consent to PROs and broad randomisation for future interventions, and met the following study-specific criteria: diagnosed with LARC (cT4, cT3 with distance to the mesorectal fascia (MRF) of $\leq$1mm and/or cN2 and/or suspicious extramesorectal lymph node metastases), tumour $\leq$10cm from the anorectal junction (MRI-based), and WHO 0-2. All patients were staged with MRI and in

accordance with the national guideline.[15] Patients with oligometastatic disease (cM1) referred for chemoradiation with curative intent were eligible. Exclusion criteria included presence of inflammatory bowel disease, prior pelvic radiotherapy, contra-indication for MRI or capecitabine, pregnancy within the last year, and inadequate understanding of the national language. At start of the study, female patients with a rectal tumour in close proximity of the vagina were excluded because of expected low coverage of the target volume. This criterion was removed in December 2015, after further clinical experience with boost planning. All patients provided written informed consent for XXXXX participation. Written informed consent for the XXXXX trial was signed by patients in the intervention group who accepted the boost intervention, according to the staged-informed consent procedure.[17]

Randomisation

After enrolment in XXXXX, eligible patients were randomly assigned (1:1) to standard chemoradiation (control group) or to a boost prior to chemoradiation (boost group). Centralised randomisation was performed by the study investigators or an authorised delegate of the Trial Office Imaging Division of the initiating institution. The allocation sequence was concealed. Patients were randomised using block randomization with variable block lengths of four-six-eight patients, stratified by centre. Neither investigators, treating physicians nor patients were blinded to treatment allocation.

Procedures

Details of the treatment protocol were described previously.[13] In both treatment arms, target volumes were delineated on planning CT-scans, but aided by T2-weighted MRI and diffusion weighted-imaging (DWI) matched to the planning CT, or positron emission tomography–computed tomography (PET-CT). Radiotherapy was administered using a Volumetric-

Modulated Arc Therapy (VMAT)-technique. Chemoradiation consisted of 50 Gy in 25 fractions of 2 Gy with concurrent capecitabine 825 mg/m^2 twice a day for five or seven days per week. The boost intervention consisted of a sequential, stereotactic boost to the tumour (excluding bowel lumen) of 15 Gy in five fractions in 5 consecutive working days without concurrent chemotherapy in the week prior to the start of chemoradiation. Delineation of the gross tumour volume (GTV) was based on T2-weighted and DWI. No clinical target volume (CTV) margin was applied around the GTV. The planning target volume (PTV) included GTV+11 mm in the anteroposterior direction, GTV+7 mm in the lateral direction and GTV+13 mm in the craniocaudal direction. These margins were derived from in-house observations on tumour movement on daily MRI scans and setup errors. A cumulative GTV dose of 65 Gy was delivered over the full treatment course of 30 fractions (6 weeks) with an equivalent dose in 2-Gy fractions of 66.3 Gy ($\alpha/\beta = 10$ Gy). The boost dose was aimed at 65 Gy with a maximal point dose of 80 Gy. Organs at risk (OAR) in the boost planning included bowel bag (excluding sigmoid), bladder, vagina and anal sphincter. OAR constraints took priority over boost dose, resulting in a lower coverage when the tumour was near one of the OARs. All patients (including controls) were treated according to the same protocol including target definition, planning and constraints, and treatment delivery. The planning constraints for the combined boost and chemoradiation treatment plan were the same as for the chemoradiation treatment plan alone. Quality assurance (QA) was performed on all radiotherapy plans using standardized methods. Boost planning and delivery were made uniformly between the two participating centres. For position verification, a cone-beam CT was performed prior to all boost fractions using the rectal wall as surrogate for tumour position and prior to the first three fractions of chemoradiation and weekly thereafter. In case of bowel distention, the patient was asked to leave the table and to empty the bowel if possible.

Timing to response assessment and surgery were included in the trial protocol. Response to treatment was evaluated with MRI at nine weeks after the last treatment fraction. Surgery was considered standard treatment and planned 12 weeks after completion of chemoradiation. Surgery took place in the institution from where the patients were referred and performed following the principles of TME, including abdominoperineal resection (APR), low anterior resection (LAR) or a rectosigmoid resection with permanent stoma (Hartmann). Several patients with a (near-)complete clinical response, based on MRI and endoscopy, were evaluated for W&W. Adjuvant treatment is not routinely administered in patients with LARC according to the national guideline.

Outcomes

The primary endpoint of the first version of the trial protocol was pCR, defined as ypT0N0. However, over time, W&W became more common in patients with a complete clinical tumour response. We therefore changed the primary endpoint into a combined endpoint of pCR in patients with planned TME at 12 weeks after the last radiotherapy fraction and, as surrogate for pCR, a 2-year sustained clinical complete response since the last radiotherapy fraction with absence of local/regional tumour regrowth in patients with W&W management, based on a previous study and the evidence that most regrowths develop within 2 years.[8,18] Patients with an ypT0Nx after local excision and no regrowth/recurrent disease within 2-years were considered complete responders. Patients with progressive disease after chemoradiation who did not receive TME were considered non-complete responders. This amendment was approved by the ethics committee in March 2017. At time of the analysis, one patient with W&W had 23 months of follow-up but was considered as a complete responder.

pCR was assessed by examination of the resected specimen in the referral hospitals of the participating hospitals and performed according to the national guidelines.[19] For patients with pCR, three levels were cut on all blocks from the tumour site and examined for presence of tumour cells. Pathologists were unaware of treatment allocation. To confirm protocol adherence, all pathology reports were reviewed by a dedicated pathologist. Follow-up for W&W took place in specialised referral centres.

Secondary outcomes included (near-)complete Mandard tumour regression grade (TRG 1-2), (near-)complete radiological MRI response, sphincter preservation, acute toxicity grade ≥3, surgical complications grade ≥3, and quality of life (QOL) during the first 12 months after randomisation. The 5-tier Mandard TRG was assessed according to the publication of Mandard and only presented in patients who received planned surgery at 12 weeks.[11] Clinical tumour response was assessed by dedicated radiologists using T2-weighted MRI and DWI at nine weeks after completion of chemoradiation and in accordance with the European Society of Gastrointestinal and Abdominal Radiology guideline for re-staging and classified in clinical complete response, complete/near complete response, residual mass (ycT1-2, ycT3 or ycT4) and lymph node restaging (ycN0 or ycN+).[20] Sphincter preservation was defined as patients who received LAR without stoma, or had a successfully reversed temporary stoma or were treated with an organ preservation strategy for 2-years. Toxicity was assessed weekly during treatment and at four and nine weeks after completion of treatment by the radiation oncologist using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Surgical complications were categorised according to Clavien-Dindo classification and included anastomotic leakage, abscess, bleeding, ileus, dehiscent fascia, iatrogenic injury to bowel and ureter/urethra, and other non-specified complications. QOL was measured with the European Organisation for Research and Treatment of Cancer (EORTC) core cancer

questionnaire (QLQ-C30) at baseline (at time of randomisation) and three, six and 12 months after.[21] Serious Adverse Events were registered for patients in the intervention arm from start of radiotherapy until eight months.

Statistical analysis

We estimated that 30% of the patients in the boost group would achieve a pCR versus 13% in the control group.[10] Patients allocated to the intervention arm may refuse the boost intervention, which will dilute the outcome in an intention-to-treat analysis.[22] The sample size was therefore adjusted for the estimated proportion of patients refusing the intervention, which was in the present trial estimated to be 20%. Considering the above, the estimated sample size was 60 patients per arm, based on a one-sided test, α=0.15, and power= 80%, corrected for a refusal rate of 20%. We used a one-sided test and higher α as recommended for phase 2 screenings trials.[23] After enrolment of the 100th patient, the refusal rate in the intervention arm was evaluated.[24] As the refusal rate was slightly higher than expected, we adapted the sample size from 120 to 128 patients.

The primary outcome was analysed with χ^2 test. Logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals (CI). Adjusted analysis was performed in case of imbalance in baseline characteristics, as suggested in the literature.[25]

Secondary objectives with a categorical outcome were analysed with χ^2 test and effect sizes were presented in OR with 95%CI. QOL was compared between the treatment groups using the EORTC QLQ-C30 summary score, which is weighted score based on 13 domains/scales of the questionnaire and captures functioning, global health and general cancer symptoms.[26] A linear mixed-model was used with a random intercept, an autoregressive covariance structure of the first order (AR1) and included time, treatment group and its interaction. Outcomes were presented in mean differences (MD) with 95%CI.

Data were analysed based on the intention-to-treat population. However, for Mandard TRG 1-2 and Clavien-Dindo surgical complications we only analysed the patients who received surgery. Differences with a p-value <0.05 were considered statistically significant, except for the primary endpoint, where p<0.15 had been pre-specified. Data were analysed with Statistical Package for Social Sciences (SPSS) version 25. An independent data and safety monitoring board (DSMB) periodically assessed safety data including radiation toxicity and surgical complications. After the first 10 patients treated with dose-escalated chemoradiation followed by LAR, enrolment of patients with a mid-rectal tumour planned for LAR, was paused for eight months to evaluate safety of the intervention in terms of anastomotic leakage.

The trial was registered with Clinicaltrials.gov, number NCTXXXXXX. The cohort is registered with the number NCTXXXXXX.

Results

Between Sept 11, 2014, and July 13, 2018, 64 patients were randomly assigned to the control group and 64 to the intervention group (Figure 1). Of the 64 patients in the intervention group, 51 (79.7%) patients accepted and underwent the intervention. Twelve (18.8%) patients refused to undergo the interventions and received standard chemoradiation. One patient accepted the intervention but did not receive a boost due to a very minimal target coverage because of the small bowel constraint. It was therefore considered unethical to have this patient come to the hospital for five additional visits.

Baseline characteristics were well balanced in terms of age, sex, presence of comorbidities, and MRF involvement (Table 1). An imbalance between the control group and boost group was observed in distally located tumours (n=36, 56.3% versus n=29, 45.3%, respectively),

cT4-stage (n=20, 31.3% versus n=11, 17.2% respectively), and cN2-stage (n=38, 59.4% versus n=45, 70.3%). The prescribed capecitabine dose was similar between the groups (3300 mg per day in each group). Median interval to MRI was nine weeks and median interval to surgery was 12 weeks in both groups.

Median tumour volume (based on the number and volume of voxels within the delineated tumour at planning CT) was comparable between the treatment groups (33 ml [IQR 20-47] in the boost arm versus 35 ml [IQR 25-57] in the control arm). Planned mean dose to the PTV of the tumour in the boost group was 66.8 Gy and in the control group 50.0 Gy (Table 2). All patients in the boost group completed the five boost fractions. Sixty (93.8%) patients completed the entire radiation schedule and 60 (93.8%) completed the prescribed capecitabine dose versus 63 (98.4%) and 61 (95.3%) in the control arm respectively. Three patients in the boost arm and one patient in the control arm missed the last treatment fraction. One patient in the boost arm missed two fractions. In two patients (boost arm), missing fractions were related to acute toxicity.

Planned surgery was received by 49 (76.6%) patients in the boost group and 53 (82.8%) patients in the control group (Table 2). In the boost group, 28 (43.8%) patients underwent LAR, 18 (28.1%) patients APR, 2 (3.1%) patients a Hartmann and 1 (1.6%) patient a local excision. In the control group, 32 (50.0%) patients underwent APR, 19 (29.7%) patients LAR, and 2 (3.1%) patients a Hartmann. Three patients in the boost group and three patients in the control group with a clinical near-complete response were evaluated for W&W but received delayed surgery because of residual tumour (none of these patients had a complete response at pathological assessment). One patient with a W&W approach in each group developed local tumour regrowth, both at one year after chemoradiation. The patient in the

boost group received salvage APR and the patient in the control group underwent a salvage local excision (ypT3) followed by completion APR. In total, nine W&W patients in the boost arm and five W&W patients in the control arm had a 2-year sustained clinical complete response. In both groups, 2 patients had distant progressive disease at time of response MRI and received palliative systemic treatment.

Pathological or 2-year sustained clinical complete tumour response rate was similar between the boost and control group: 23 of 64 (35.9%, 95%CI 24.3-48.9) in the intervention group versus 24 of 64 (37.5%, 95%CI 25.7-50.5) in the control group; OR=0.94 [95%CI 0.46-1.92], p=0.86. In the boost group, 13 patients had a pCR, nine patients had a W&W with a 2-year sustained clinical complete response, and one patient had an ypT0Nx after a local excision with 2-year freedom of regrowth/recurrent disease. In the control group, 19 patients had a pCR and five patients had a W&W with a 2-year sustained clinical complete response.
A multivariable analysis including treatment allocation and the imbalanced baseline characteristics (i.e. cT-stage, cN-stage and tumour location) showed no significant effect of any of the factors nor a significant primary outcome (Supplement Data File 1). The per protocol analysis showed a pathological or 2-year sustained clinical complete tumour response in 18/51 (35.3%) patients treated with dose-escalated chemoradiation and 29/77 (37.7%) patients treated with standard chemoradiation; OR=0.90 [95%CI 0.43-1.89], p=0.79.

Clinical complete/near-complete tumour response (i.e. ycT0(near)ycN0) at MRI was not significantly different between the groups: 18 of 64 (28.6%) patients in the boost group versus 12 of 64 (18.8%) in the control group; OR=1.73 [95%CI 0.75-3.98] (Table 3 and Supplement Data File 4).

Sphincter preservation was more often achieved in the boost group than in the control group: 36 of 64 (56.3%) versus 22 of 64 (34.4%); OR=2.46 [95%CI 1.20-5.01] (Table 3).

Of all patients who underwent planned surgery, a higher rate of (near-)complete tumour regression was observed in the boost group compared with the control group: Mandard TRG 1-2 in 34 of 49 (69.4%) versus 24 of 53 (45.3%) in the control group: OR=2.74 [95%CI 1.21-6.18] (Table 3 and Supplement Data File 3).

The most common CTCAE acute toxicities included diarrhoea/proctitis, fatigue, dermatitis and cystitis non-infectious (Figure 2). Grade $\geq$3 toxicity was comparable between the groups: 6 of 64 (9.4%) in the boost group versus 5 of 64 (7.8%) in the control group: OR=1.22 [95%CI 0.35-4.22) (Table 3). The proportion of patients with diarrhoea/proctitis toxicity grade 1-2 in the boost group was higher (57.8% versus 42.4% in the control group). Two patients in the boost arm had grade 4 toxicity. One patient developed capecitabine-related pan enteritis and was admitted to the intensive care (no DPD deficiency was demonstrated). One patient with mucosal bleeding developed acute renal failure after contrast injection for CT, which was temporarily treated with dialysis. None of the patients in the control arm developed grade 4 acute toxicity. No grade 5 toxicity was observed.

Of all patients who underwent surgery, occurrence of Clavien-Dindo grade >3 surgical complications was not statistically significant between the groups: 14 of 53 (26.4%) in the boost group versus 11 of 57 (19.3%) in the control group: OR=1.50 [95%CI 0.61-3.68] (Table 3). One (1.6%) patient in the boost group died due to a cardio/pulmonary event <30 days after APR with partial sacrum resection which was judged not to be related to the boost intervention.

EORTC QLQ-C30 response rates at the different time points ranged between 68.8% and 92.2% in the boost group and 67.2% and 89.1% in the control group. The summary score showed a significantly lower score in the boost group at 3 months after randomisation (MD with the control group = -7.5 [95%CI 3.0-12.1]; p=0.001) (Table 3 and Figure 3). At baseline, 6 and 12 months QOL was comparable between the groups.

Discussion

This trial may indicate that a radiotherapy boost of 15 Gy to the tumour prior to standard dose chemoradiation does not lead to more pathological or sustained clinical complete tumour responses in patients with LARC. However, significantly more (near-)complete tumour regression (Mandard TRG 1-2) and sphincter preservation was observed in the dose-escalated chemoradiation group. Severe acute toxicity and surgical complications were comparable between both groups but QOL was worse at 3 months after randomisation in the boost group.

In a previous publication, a clear dose-response relationship in LARC was demonstrated for tumour regression after preoperative chemoradiation for tumour dose levels in the range of 50.4-70 Gy.[10] In contrast, we observed no increase in complete response rate following dose-escalation from 50 to 65 Gy. The study in question was partly based on data from a randomised phase 3 trial, where the addition of brachytherapy boost to standard dose chemoradiation did increase the rate of complete and near-complete response, but not the rate of pCR.[27] The subsequently estimated dose-response curve used ordinal logistic regression for assessing the relationship between dose and TRGs 1-4 (not specifically on pCR). The reported dose-response association may thus mainly be driven by TRG 1-2, which would support our findings. Yet, it remains unclear why dose escalation leads to more tumour

regression but not a complete response. In the present trial, it might partly be explained by the limited boost dose to the PTV of the tumour due to its location near one of the OARs (as shown by the minimum dose) which could have diluted the boost effect. Time between the completion of chemoradiation and (pathological) response assessment could also play a role, suggesting that TRG 2 may become TRG 1 by awaiting further response, as previously supported.[28,29]

Surprisingly, the rate of complete response after standard chemoradiation which we observed was much higher than reported in literature, especially considering the advanced stage.[3,4] This may partly be explained by tumour size. Tumour volume, as well as nodal stage, has an effect on the dose-response relationship, with smaller volume tumours and absence of pathological lymph nodes demonstrating higher probability of tumour regression.[10] In the present trial, patients had a median tumour volume of 35 ml (comparable between the groups), which is relatively small compared for example with the previously discussed phase 3 trial.[27] The national colorectal cancer screening programme aims to detect (advanced) tumours earlier which may have led to smaller tumour volumes compared with those observed in historical cohorts. Nodal stage is rather unlikely to explain the high response rate as most of the patients participating in this trial had node positive disease. In addition, quality of diagnostic MRI differs among studies and has improved over the past years which could have resulted in stage migration. The 12-week time interval to surgery may also partly explain the high response rate. Several studies have shown a positive association between time interval and pCR.[3,4] Thus simply on the basis of the 12 week interval from end of radiotherapy to surgery, compared to the 6-8 weeks most commonly used, one would expect the complete response rate to be higher than in other trials.[12,30]

Acute toxicity grade 3-4 was similar between the treatment arms and comparable with literature.[12] Nevertheless, more grade 1-2 toxicity was observed in the boost arm, mainly bowel-related toxicity including proctitis, diarrhoea and mucosal bleeding. Patients in the boost group had a lower QOL at 3 months after randomisation. Nevertheless, this effect was temporary, and the two groups were equivalent at 6 and 12 months. The effect could have been affected by the non-blinded nature of the trial.

We observed a higher rate of sphincter preservation in the boost group than in the control group. This is a promising finding because a permanent stoma can affect patients' life severely. However, this outcome should be interpreted with caution as there is likely selection bias associated. At the time of the present trial, organ preservation was not actively offered by all surgeons to all patients with a clinical complete response. As result, (non)surgical treatment was very much based on preference and not on the effect of the treatment or intervention. Furthermore, the control group was not informed about the present trial and may therefore have had less awareness about the possibility of organ preservation after a clinical complete response.

The results of this trial are in line with previous randomised trials.[27,31] Published recently, the INTERACT trial was a phase 3 trial investigating the effect of an integrated radiation boost (10x 1 Gy) during chemoradiation versus chemoradiation with oxaliplatin on Mandard TRG 1-2 in LARC. The TRG 1-2 rate was significantly higher in the radiation boost group (62% versus 52%) and pCR rate was similar (24% in both groups). Nevertheless, the INTERACT trial excluded cT4, used a lower boost dose, performed surgery earlier (after 7–9 weeks), and did not include a standard treatment group, which makes the trials less comparable. The earlier mentioned Danish phase 3 trial observed a similar pCR rate between the dose-

escalated chemoradiation group and the standard arm (18% in both groups) but more TRG 1-2 (44% versus 28%).[27] Some nonrandomised studies have shown high complete response rates in selected LARC patients with endorectal radiation techniques including high dose rate endorectal brachytherapy or X-ray contact therapy.[32,33] This is likely the result of the higher radiation dose achieved within the tumour using these techniques. Unfortunately, endorectal radiation may not be suitable for large tumours and are associated with bleeding toxicity.

This trial has several limitations. Randomisation was not stratified by clinical tumour characteristics, which resulted in differences between the groups in cT-stage, cN-stage and tumour location and the choice for adjusted analysis. Also, we re-defined the endpoint because progress in organ-sparing treatment approaches had caught up with our primary stated endpoint. However, 2-year freedom of local/regional regrowth may not directly translate into pCR. Patients with a clinical complete response may have still had scattered tumour cells which are easily missed at response assessment. Instead, a patient-centred outcome should be preferred, i.e. clinical complete response leading to organ-preservation. This would have required all patients to be evaluated for organ-preservation prior to surgery, which was not the case. These results can therefore not be used to determine the impact of a radiotherapy boost on organ preservation.

Conclusions

The XXXX trial may indicate that dose-escalated chemoradiation with a radiotherapy boost of 15 Gy to the tumour does not lead to more pathological or sustained clinical complete tumour responses in LARC. We therefore suggest that the investigated dose-escalation strategy has currently no role in the setting of neoadjuvant chemoradiation with planned surgery in LARC patients. However, we showed a high rate of (near)complete tumour

regression following dose-escalated chemoradiation which encourages further investigation of the use of radiotherapy to render more patients for organ preservation.

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Figure headings

Figure 1. Flowchart of eligible and randomised patients.

Figure 2. CTCAE acute toxicity by allocated treatment.

Figure 3. EORTC QLQ-C30 quality of life summary score by allocated treatment at randomisation, and 3, 6 and 12 months after. The summary score is a weighted score of 13 items of the questionnaire and captures functioning, global health and general cancer symptoms. Statistically significant difference between the boost group and control group is denoted with an asterisk (*).

Table 1. Baseline characteristics by allocated treatment.

Baseline characteristics	Boost group (n=64)	Control group (n=64)
Age, years	64.5 [55.0 – 69.0]	62.0 [56.0 – 71.0]
Sex		
Male	48 (75.0)	47 (73.4)
Female	16 (25.0)	17 (26.6)
Comorbidities		
None	30 (46.9)	26 (40.6)
1 or more	34 (53.1)	38 (59.4)
Tumour distance*		
≤3.0cm	29 (45.3)	36 (56.3)
3.1-5.0 cm	12 (18.8)	8 (12.5)
5.1-10.0cm	23 (35.9)	20 (31.2)
Tumour stage		
cT2	2 (3.1)	5 (7.8)
cT3	51 (79.7)	39 (60.9)
cT4	11 (17.2)	20 (31.3)
Distance to the mesorectal fascia‡		
≤1 mm	42 (65.6)	46 (71.9)
>1 mm	22 (34.4)	18 (28.1)
Nodal stage		
cN0	5 (7.8)	9 (14.1)
cN1	14 (21.9)	17 (26.6)
cN2	45 (70.3)	38 (59.4)
Oligometastatic disease		
No	61 (95.3)	62 (96.9)
Yes	3 (4.7)	2 (3.1)
Capecitabine prescribed dose, mg per day	3300 [3000 – 3600]	3300 [3000 – 3300]
Interval to MRI, weeks†	9.0 [8.0-9.0]	9.0 [8.0-9.0]
Interval to surgery, weeks	12.0 [12.0 – 14.0]	12.0 [11.0 – 13.0]

Data presented in number (%) or median [interquartile range].

‡ Based on the primary tumour.

***** Measured from the anorectal junction on sagittal MRI.

† One patient in the boost group did not undergo the response MRI because of anxiety symptoms.

Table 2. Treatment course by allocated treatment.

Treatment characteristics	Boost group (n=64)	Control group (n=64)
Mean PTV_{tumour} dose, Gy[#]	66.8 [60.1-69.8]	50.0 [49.9-50.2]
Minimum PTV_{tumour} dose, Gy[‡]	58.9 [50.5-64.3]	48.6 [48.3-48.8]
Maximum PTV_{tumour} dose, Gy[‡]	74.0 [65.6-75.1]	51.4 [51.2-51.8]
Radiotherapy fractions completed	60 (93.8)	63 (98.4)
Prescribed capecitabine dose completed	60 (93.8)	61 (95.3)
Planned surgery		
Low anterior resection	28 (43.8)	19 (29.7)
Abdominoperineal resection	18 (28.1)	32 (50.0)
Hartmann resection	2 (3.1)	2 (3.1)
Local excision	1 (1.6)	0
Delayed/salvage surgery[†]		
Low anterior resection	1 (1.6)	2 (3.1)
Abdominoperineal resection	1 (1.6)	2 (3.1)
Local excision	2 (3.1)	0
2-year watch-and-wait	9 (14.1)	5 (7.8)
Palliative systemic treatment	2 (3.1)	2 (3.1)

Data presented as median [interquartile range] or n (%). PTV_{tumour} = planned target volume of the tumour.

[#] Planned mean dose to the PTV.

[‡] Minimum dose is the highest dose received by 99% of the PTV (D99) and the maximum dose is the highest dose received by 1% of the PTV (D1).

[†] Includes patients with a (near)complete clinical response after chemoradiation and evaluated for a watch-and-wait strategy but who received surgery because of a non-sustained complete response at first watch-and-wait follow-up assessment (referred to as delayed surgery for near-complete responders) or at later follow-up assessment (referred to as salvage surgery for regrowth).

Table 3. Primary outcome and secondary outcomes by allocated treatment.

Outcomes	Boost group (n=64)	Control group (n=64)	OR or MD (95% CI) boost vs. control	P value*
pCR or 2-year cCR	23 of 64 (35.9)	24 of 64 (37.5)	0.94 (0.46-1.92)	0.86
ycT0(near)ycN0 at response MRI‡	18 of 64 (28.1)	12 of 64 (18.8)	1.73 (0.75-3.98)	0.21
Sphincter preservation	36 of 64 (56.3)	22 of 64 (34.4)	2.46 (1.20-5.01)	0.01
Mandard TRG 1-2#	34 of 49 (69.4)	24 of 53 (45.3)	2.74 (1.21-6.18)	0.02
CTCAE grade ≥3	6 of 64 (9.4)	5 of 64 (7.8)	1.22 (0.35-4.22)	0.75
Clavien-Dindo grade ≥3	14 of 53 (26.4)	11 of 57 (19.3)	1.50 (0.61-3.68)	0.50
QoL summary score†				
Baseline	87.7 (1.6)	86.3 (1.6)	1.31 (-5.81 to 3.18)	0.57
3 months	80.8 (1.6)	88.4 (1.7)	-7.54 (-12.09 to -2.99)	0.001
6 months	78.5 (1.7)	82.2 (1.7)	-3.64 (-8.28 to 1.00)	0.12
12 months	87.0 (1.8)	87.5 (1.8)	-0.57 (-5.56 to 4.42)	0.82

Data presented as n (%) and in mean (standard error) for quality of life scores.

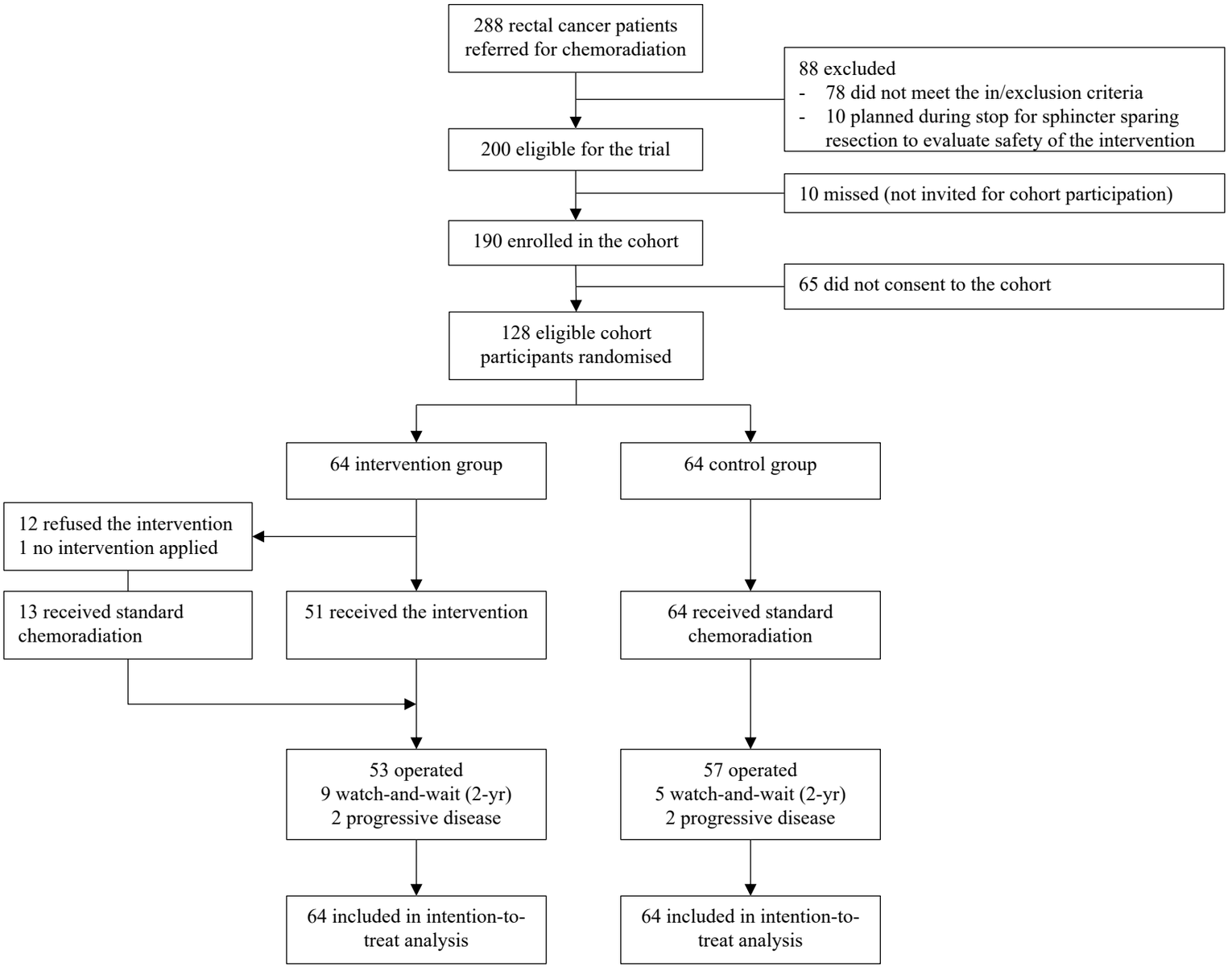
cCR = clinical complete response. CI = confidence interval. CTCAE = common terminology criteria for adverse events. MD = mean difference. OR = odds ratio. pCR = pathological complete response. QoL = quality of life. Ref = reference group. TRG = tumour regression grade.

* Based on X^2 test.

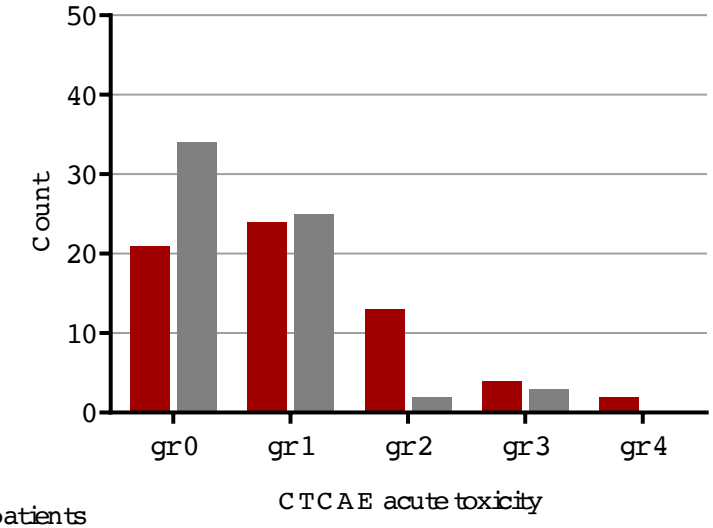
Presented in patients treated with planned surgery at 12 weeks

‡ One patient in the boost group did not receive a response MRI because of new-onset claustrophobia.

† Presented as mean difference (95% confidence interval).

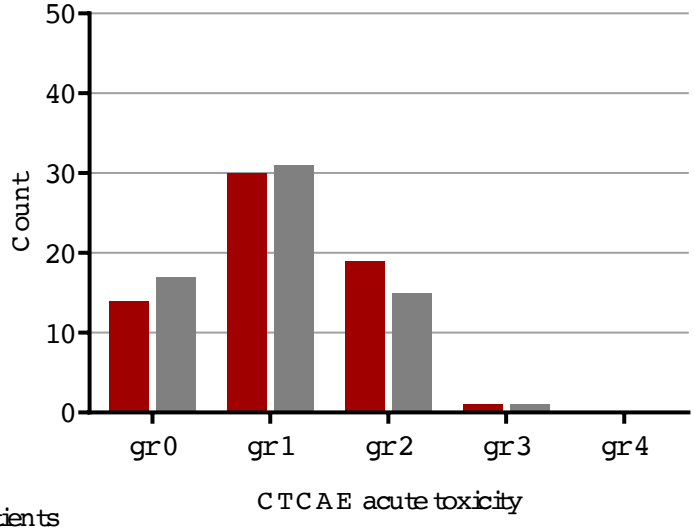

288 rectal cancer patients referred for chemoradiation
88 excluded
- 78 did not meet the in/exclusion criteria
- 10 planned during stop for sphincter sparing resection to evaluate safety of the intervention
200 eligible for the trial
10 missed (not invited for cohort participation)
190 enrolled in the cohort
65 did not consent to the cohort
128 eligible cohort participants randomised
64 intervention group
64 control group
12 refused the intervention
1 no intervention applied
13 received standard chemoradiation
51 received the intervention
64 received standard chemoradiation
53 operated
9 watch-and-wait (2-yr)
2 progressive disease
57 operated
5 watch-and-wait (2-yr)
2 progressive disease
64 included in intention-to-treat analysis
64 included in intention-to-treat analysis

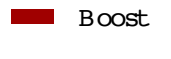
Diarrhoea/proctitis



Nr of patients					
Boost	21	24	13	4	2
Control	34	25	2	3	0

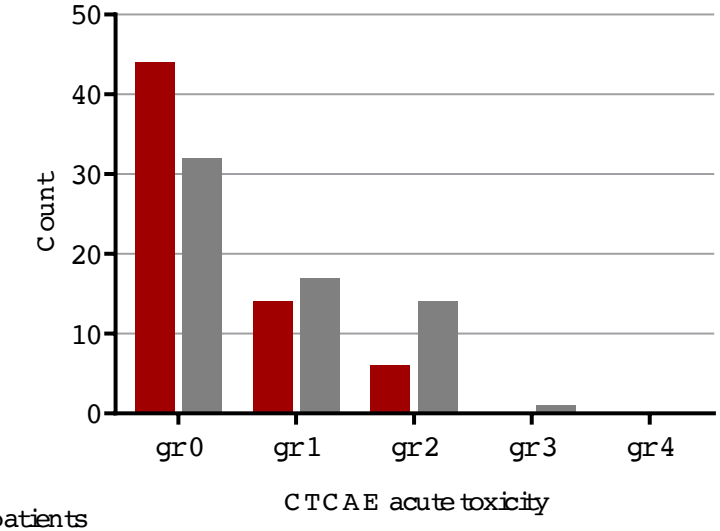
Fatigue





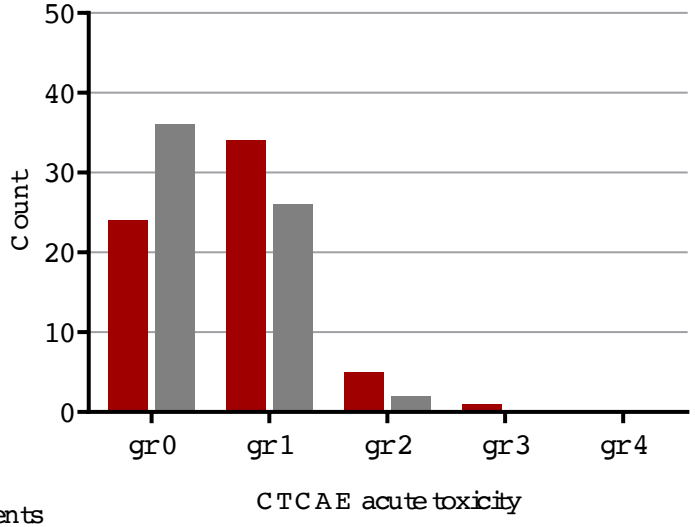
Nr of patients					
Boost	14	30	19	1	0
Control	17	31	15	1	0

Dermatitis

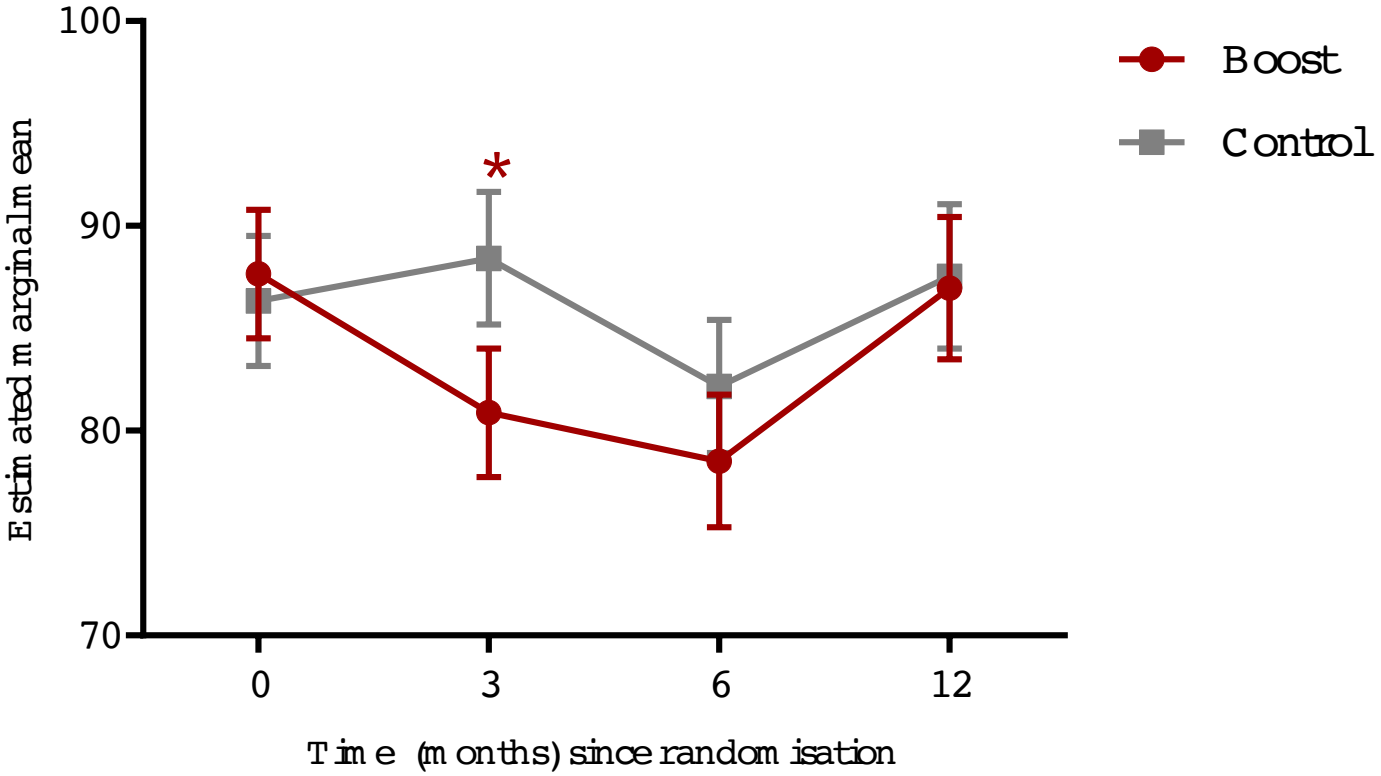


Nr of patients					
Boost	44	14	6	0	0
Control	32	17	14	1	0

Cystitis non-infectious



Nr of patients					
Boost	24	34	5	1	0
Control	36	26	2	0	0



Nr of patients				
Boost	59	58	53	44
Control	57	54	53	43

Supplementary Data

- **Table A1**. Multivariable analysis of the primary outcome adjusted for clinical tumour stage, clinical nodal stage and tumour location.
- **Table B1.** Mandard tumour regression grades in patients with planned surgery at 12 weeks after the completion of chemoradiation by treatment allocation.
- **Table C1.** Radiological tumour response at MRI planned at 9 weeks after the completion of chemoradiation by treatment allocation.

Table A1. Multivariable analysis of the primary outcome adjusted for clinical tumour stage, clinical nodal stage and tumour location.

			95% CI		
		OR	**Lower**	**Higher**	**p-value**
Treatment	Boost	0.99	0.47	2.09	0.98
	Control	Ref			
Tumour location	6-10cm	1.10	0.48	2.53	0.92
	3-6cm	0.95	0.31	2.88	0.93
	≤3cm	Ref.			
Tumour stage	cT2	1.75	0.30	10.14	0.53
	cT3	1.19	0.45	3.15	0.72
	cT4	Ref.			
Nodal stage	cN0	2.83	0.78	10.28	0.11
	cN1	0.90	0.36	2.24	0.83
	cN2	Ref.			

CI = confidence interval. OR = odds ratio. Ref = reference group.

Table B1. Mandard tumour regression grades in patients with planned surgery at 12 weeks after the completion of chemoradiation by treatment allocation.

Tumour regression grade	Boost group (n=49)	Control group (n=53)
Complete response, TRG 1	16 (32.7)	19 (35.8)
Fibrosis with scattered tumour cells, TRG 2	18 (36.7)	5 (9.4)
Fibrosis outgrowing residual cancer, TRG 3	12 (24.5)	17 (32.1)
Residual cancer outgrowing fibrosis, TRG 4	2 (4.1)	12 (22.6)
Absence of regressive change, TRG 5	1 (2.0)	0

Data presented as n (%). TRG = tumour regression grade.

Table C1. Radiological tumour response at MRI planned at 9 weeks after the completion of chemoradiation by treatment allocation.

Clinical tumour response	Boost group (n=64)	Control group (n=64)
Tumour staging		
ycT0(near)[*]	19 (30.1)	12 (18.7)
ycT1-2	6 (9.5)	8 (12.5)
ycT3	34 (54.0)	33 (51.6)
ycT4	4 (6.3)	11 (17.2)
Missing[†]	1 (1.6)	0
Lymph node staging		
ycN0	42 (66.7)	40 (62.5)
ycN+	21 (33.3)	24 (37.5)
Missing[†]	1 (1.6)	0

Data presented as n (%).

[*] Complete / near complete tumour response

[†] One patient in the boost group did not undergo the response MRI because of anxiety symptoms.